

Appln No.: 09/786,502
Amendment Dated: September 8, 2003
Reply to Office Action of March 6, 2003

REMARKS/ARGUMENTS

This is in response to the Office Action mailed March 6, 2003 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Applicants request an extension of time and enclose the appropriate fee. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

The Examiner maintained the restrictions requirement, stating that the fusions peptides and the nucleotides were separate and distinct inventions (a standard which is not applied under PCT Unity of Invention practice), and stating that "PCT rules for lack of unity do not allow for examination of multiple products." Applicants submit that this latter position is incorrect. Indeed, the Administrative Instructions Under the PCT has an entire section which discusses unity of invention for claims in the same category (i.e, two sets of product claims) which was attached to the response to the restriction requirement. Among the specific examples given is Example 17 which states that claims to Protein X and a DNA sequence encoding protein X share unity of invention. Accordingly, Applicants request reconsideration of the restriction requirement and consideration of all claims, or in the alternative, a statement of why the Examiner considers the Administrative Instructions to be inapplicable in this case so that meaningful review by way of petition can be had.

The Examiner indicated the sequence rules were not complied with. Applicants have filed a sequence listing electronically to avoid damage to the CRF and enclose a paper copy of the sequence listing. Entry of the paper copy in the application is requested. The undersigned certifies that the paper copy has the same content as the electronically filed sequence listing.

The Examiner rejected claims 1-6 and 17-20 under 35 USC § 112, second paragraph. Claim 1 has been amended in accordance with the Examiner's suggestions. Claim 4, and the corresponding part of the specification have also been amended in view of the Examiner's remarks. However, the Examiner has not provided any reason why a person skilled in the art would have any difficulty determining the scope of claim 4 as presently drafted, given the fact that the sequence of CD28 is known. (See for example the GenBank NM_006139, a copy of which is attached). Further, the Examiner has not cited any legal basis for the statement that "claim 4 is indefinite because it refers to specific amino acid residues without a reference [to] a specific amino acid sequence having a sequence identifier." The sequence rules only provide that where a sequence is provided in the form of a listing of specific bases, it must have a sequence ID number. They do not create a substantive obligation on the applicant to provide such information for everything that could be presented as a sequence listing. The suggestion of the

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Examiner to import an additional sequence listing is therefore declined in the absence of specific explanation showing that the claim is in fact indefinite.

The Examiner has rejected claims 3-5 and 18-20 under 35 USC § 112, first paragraph, stating that these claims lack enablement because of the reference to cytoplasmic domains being "derived from" CD28 or 41-BB. Claims 3 and 5 have been amended in accordance with the Examiner's suggestion. This amendment is believed to fully overcome the rejection. It should be noted that the language of claim 3 and 5 does not exclude additional portions of CD28 or 41-BB beyond the cytoplasmic domain.

The Examiner rejected the claims as obvious over various combinations of references, including Eshhar (US 2002/0137697). Applicants point out that this application is a pre-PGPUB application by virtue of its PCT filing date. Thus, the citation of Eshhar US 2002/0137697 against this application is inappropriate. However, Applicants also advise the Examiner that the ultimate parent application on which this publication relies has issued as US Patent Nos. 6,175,345 and 6,373,455, and that PCT publications WO93/19163 and WO 97/15669 exist in the same family. The Examiner may wish to substitute one of these publications should the rejection be maintained.

Looking at the merits of the rejections, it is apparent that the Examiner has scanned the art, locating the bits and pieces of the present invention, and then states that the particular combinations which are the subject matter of this invention are obvious. Applicants respectfully submit that such a piece meal approach, with its necessary reliance on hindsight, is inappropriate, and that the rejection should therefore be withdrawn.

The claims are directed to fusion protein compositions that comprises an scFv that binds to PSMA connected, optionally via a connector, to the cytoplasmic domain of a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor. In claims 2 and 3, the source of the cytoplasmic domain is specified, and in claim 4 the specific portion of the CD28 cytoplasmic domain is specified.

The Examiner argues that Eshhar teaches everything in these claims except PSMA as the scFv portion of the fusion, and that using a PSMA scFV is obvious because of teaching in Murphy I and II about the existence of PSMA antibodies and its possible role as a target of therapy. As a first matter, it must be noted that this characterization of the art is erroneous because Eshhar also does not teach the specific sequence recited in claim 4. Thus, the rejection as it relates to claim 4 is plainly incomplete because no argument is made with respect to the limitations of this claim. Furthermore, the Murphy references do not teach a PSMA-specific scFv.

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More significantly, however, the Examiner has failed to establish, or even to say anything about, any reasons why the art provides an expectation of success, as opposed to some vague invitation to try a variation of the Eshhar teaching that would fall within the scope of the present claims. As noted in the present application, tests showing IL-2 stimulation, while suggestive of utility, are not dispositive since they may be followed by T cell anergy or apoptosis. This results in T cell death *in vivo* rather than the development of an appropriate immune response. (Page 3, lines 31-33; Page 14, lines 47) Insufficient costimulatory signals and perhaps other problems can render a composition effectively useless if the cells expressing the fusion does not remain alive, undergo proliferation and respond when a restimulation occurs. Eshhar, however, does not demonstrate such activity, and art such as the Altermansmidt article (cited on Page 14) show that it may not be presumed for different antibodies than the one tested in Eshhar. The present application does demonstrate this activity for PSMA-containing species. This is a patentable and unobvious advance over the art which teaches at best techniques, and not the claimed invention.

With respect to the specific recitation in claims 6, and 17-19 of the incorporation of a CD98 hinge section as the connector, the Examiner cites a reference which uses a different scFv from the claimed invention, a γ receptor domain and a CD8 hinge. The Examiner's entire argument is that because the CD8 hinge is used in this molecule, putting it in any other fusion, including that now being claimed would have been obvious. The Examiner has not, however, pointed to any suggestion in the references that the CD8 hinge is of such general applicability, nor explained why such applicability would be expected based on what is taught. Thus, the Examiner has merely found the pieces of the claimed invention in the art and has not made the connections required to support an obviousness rejection. See, *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988) ("Citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious.").

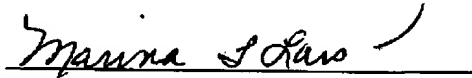
The Examiner has made similar rejections of claims 1-4, 6 and 17-19 substituting US Patent No. 5,369,046 of Capon for the Eshhar disclosure. The Examiner characterizes the Capon disclosure as being comparable to that of Eshhar. If this characterization were accurate, these rejections would suffer from the same difficulties as those based on Eshhar. In fact, however, the antibodies described in Capon are not formed from antibodies that have just the variable regions, but rather include substantial amounts of the constant regions (CH1, CH2 etc). The usage in the Capon patent of the term "single chain antibody" is inconsistent with accepted usage in which the term scFv is defined as "scFv: A single chain molecule composed of the variable regions of an antibody heavy and light chain joined together by a flexible linker." <http://www.roitt.com/glossary.htm#s>. Thus, the Capon reference is even less similar to the claimed invention than Eshhar.

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With respect to claims 5 and 20 that recites 4-1BB as the cytoplasmic domain, the Examiner has cited Eshhar or Capon, the Murphy and Darcy references, and a further reference of Alderson. This reference does little more than state that 4-1BB is known, and is plainly an example of using hindsight to interpret the reference. Based solely on the abstract of Alderson, the Examiner states that the reference teaches that 4-1BB is a T-cell receptor. What the abstract actually states is that 4-1BB is shown to be a member of the tumor necrosis factor receptor family. Since the motivation to use 4-1BB is based on the identification of it as a T cell receptor, it is necessary for the Examiner to provide an explanation of why one skilled in the art would equate a TNF receptor with the receptors of the Eshhar or Capon references. This has not been done. Furthermore, even with such an explanation, the rejection would still suffer from the same flaw as discussed above. Furthermore, the Examiner states that the reference discloses the sequence of 4-1BB, although there is no statement in the abstract, nor even a statement that the full paper discloses the sequence. The basis for this statement of the Examiner is therefore not understood.

For these reasons, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully Submitted,



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